REMARKS

The present Amendment is in response to the Examiner's Office Action mailed November 28, 2003. Claims 28-46 are pending in the application. By this Amendment, claim 28 is amended.

By this amendment, independent claim 28 has been amended to more clearly define the claimed invention. Support for the amended and new claims are discussed below. No new matter has been added. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

Claims 28-46 are currently under consideration. Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience, Applicant's remarks are presented in the order in which they were raised in the Office Action.

I. Interview with the Examiner

Applicant thanks Examiners J. Friedman and B.J. Forman for an in-person interview on February 2, 2004. Applicant appreciates the opportunity to explain the novel features of his invention and the many helpful suggestions by the Examiners. Applicant also thanks Examiner Forman for a telephonic interview on February 27, 2004; Supervisor Gary Benzion for a telephonic interview on March 30, 2004; and Supervisor Gary Benzion and Examiner Forman a telephonic interview on April 22, 2004, with Applicant's representatives. The present amendment reflects the discussions that took place during the interviews.

II. Claim amendments

Claim 28 is amended to provide a clearer definition of the claimed invention.

Claim 28, as amended, specifies "detecting at the distinct location on the microarray after a single round of hybridization, stable hybrids formed during the incubation wherein a hybridization signal indicating the formation of a hybrid or lack of formation of a hybrid genotypes the individual." Support for the amendment can be found in the specification at page 13, lines 17-19, page 14, line 5 – page 15, line 21, page 16, lines 2-6 and Figures 3, 4 and 5 *inter alia*. In particular,

Figure 5 and page 15, lines 8-21, describe the genotyping (including homozygosity and heterozygosity) of the individual based on the hybridization signal at the distinct location. The amendment reorders the locations of various phrases in the prior version of the claim for the sake of clarity and no new matter is introduced. Applicants thank the Examiner for suggesting use of the term "genotypes" in the claim.

Amendments replacing "those" with "polynucleotide sequences" and "oligonucleotides in the probe mixture consist of oligonucleotides of known sequence and length and having sequences" with "oligonucleotides in the probe mixture are of known sequence and length and have sequences" are for the sake of clarity and do not include any new matter. (emphasis added).

Claim 28 is amended to include the limitation of "*amplified* polynucleotides comprising a defined *genomic* segment" in addition to all the elements of claim 28. (emphasis added). Support for the amendment can be found in the Specification as follows:

Page 2, line 28 – page 3 line of the Specification states that: "genomic segments from multiple samples are amplified using polymerase chain reaction primers, where each genomic segment contains a genetic locus, that is, a DNA marker of interest. The genomic segments are formed into a microarray on a surface where the material at each location of the surface corresponds essentially to a single genomic segment from a single sample." Further support for the amendment is found on page 4, lines 22 – 27 ("[a] specific pair of primers is used for each genomic segment of interest, that is for each genomic segment containing a known potential mutation or other DNA alteration of interest"); page 5, lines 9 – 11 ("each amplicon associated with a specific genomic segment from a specific individual, each genomic segment containing a genetic locus of interest"); and page 10, lines 16 – 25 and Table 1.

Claim 28 as amended, further specifies samples on the microarray "occupying an area smaller than about 1 square millimeter." Support for this amendment is found in Figures 3A, 3B, 4A and 4B and page 3, lines 28-29 ("space bar corresponds to 1.0 mm"). Examples of individual spots of 100 μm are found on page 6, line 6 and page 12, line 5 of the Specification. No new matter is added.

III. Claim Rejections Under 35 U.S.C. § 102

(a) Gilles et al.

Claims 28-33, 36-39, 41-43 and 46 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Gilles et al. (Nature Biotechnology, April 1999, 17: 365-370). The Examiner cites Gilles for disclosing a method of simultaneously genotyping multiple samples, wherein the method comprises a single round of hybridization.

Applicants submit that Gilles does not teach or suggest "detecting at the distinct location on the microarray after a single round of hybridization, stable hybrids formed during the incubation wherein a hybridization signal indicating the formation of a hybrid or lack of formation of a hybrid genotypes the individual" as specified in amended claim 28.

As illustrated in Figures 1 and 2 and page 370, left column, Gilles discloses individual hybridizations at each distinct location. Detecting hybridization at each distinct location does not genotype the sample, instead the combined result of hybridization events at (at least) four different locations (corresponding to wild type, mutant and two mismatches) is required to genotype the sample. To obtain a complete set of information for genotyping "[t]he second, third, and fourth reporter groups were applied in the same row-wise manner" as stated in Gilles on page 370 ("Electronic hybridization").

In contrast, claim 28, as amended, specifies "detecting at the distinct location on the microarray after a single round of hybridization genotypes the individual." Since Gilles does not teach or suggest each every element of claim 28 (as amended) and claims 29-33, 36-39, 41-43 and 46 depend from independent claim 28, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Gilles also fails to teach the probe mixture of the present invention. As shown in Figure 1, Gilles teaches a probe mixture that contains mismatched reporter sequences which are related to the gene and allelic variant but are not complementary to either the gene or allelic variant present in any specific location on the microarray as they contain additional variations. As shown in Figure 2, the mismatched sequences are an essential feature of the method disclosed in Gilles since the

mismatched probes are used as negative controls to establish the background of the array before a hybridization signal is read. In contrast, independent claim 28 specifies "oligonucleotides in the probe mixture ... having sequences specifically complementary to polynucleotide sequences within the defined segments." (emphasis added). Independent claims 28 further specifies that hybridization conditions "allows discrimination at single nucleotide resolution." Thus, the presence of *mismatched* oligonucleotides in the probe mixture of Gilles teach away from the probe mixture of the present invention where the oligonucleotides "are selected from the group consisting of oligonucleotides with sequences [specifically] complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene," as specified in independent claim 28.

Therefore, Applicant submits that Gilles et al. does not anticipate claims 28-33, 36-39, 41-43, and 46 and respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

(b) Shuber

Claims 28-34, 36-39, 41-42 and 46 stand rejected under 35 U.S.C. 102(b) as being anticipated by Shuber (U.S. Patent No. 5,834,181, issued 10 November 1998). The Examiner cites Shuber for disclosing a method of simultaneously genotyping multiple samples. The Examiner asserts that Shuber teaches genotype determination by hybridization signal detection and cites column 25, lines 12-24 in support of her position.

Shuber at column 25, lines 12-24, states that while bound ASOs can be detected as "having been bound prior to separation", Shuber then refers to Examples 2 and 3 to state that "after separation, the ASO can be positively identified by measuring emission wavelength in response to fluor excitation." (emphasis added; Shuber, Column 25, lines 18-23.) Shuber suggests modifying the method of Example 2 by using a unique fluorescent label for each probe to detect 106 mutations. Example 2 teaches that samples are deposited as dot blots on Biotrans membranes and are eluted for sequencing in order to determine the genotype. Example 3 teaches the excision of positive spots for separating the positive ASOs. (Shuber col. 20, lines 16-55). Since Shuber teaches the use of simultaneously hybridizing "a complex mixture of hundreds of mutation-specific oligonucleotides" (col. 27, lines 40-44), Shuber's method requires the separation and individual analysis by

sequencing or measurement of fluorescent emission of each of the hybridized ASOs. Shuber does not teach a method where the sample may be genotyped by detecting a signal at a distinct location on the microarray.

In contrast to Shuber, claim 28, as amended, specifies "detecting at the distinct location on the microarray after a single round of hybridization genotypes the individual." Since Shuber does not teach or suggest each every element of claim 28 (as amended), and claims 29-33, 36-39, 41-43 and 46 depend from independent claim 28, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Shuber teaches allele-specific oligonucleotides (ASOs) representing known cystic fibrosis mutations. (*See* table beginning at the bottom of column 18 and continuing into column 19.) The oligonucleotide sequences taught in these tables correspond to separate, distinct and non-overlapping wild type and mutant sequences distributed along the length of the cystic fibrosis gene; there are no sets of oligonucleotides including the sequences of wild type and variants of the gene corresponding to a particular locus.

Claim 28 as amended specifies, "oligonucleotides are selected from the group consisting of oligonucleotides with sequences complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene." The probe mixture in the Shuber reference fails to teach a probe mixture consisting of "a gene and one or more allelic variants of the gene." Thus, Shuber fails to teach each and every element of claim 28.

Claim 28, as amended, further specifies "each sample in a distinct location and occupying an area smaller than about 1 square millimeter." Applicant submits that a sample cannot be placed in a membrane support within an area "occupying an area smaller than about 1 square millimeter." In support, Applicant submits two references:

(i) a citation stating that dots in microarrays "may be anywhere from 25-500μm in diameter. As of this writing, most DNA microarray dots are 100 μm ± 50 μm in diameter." (*see* page 18, third paragraph; Schermer, M.J. Ch. 2: Confocal scanning microscopy in microarray detection. pp. 17-42

in *DNA Microarrays: A Practical Approach* ed. M. Schena, Oxford University Press Inc., New York, 1999).

(ii) a section entitled "Microscopic Element" from the textbook on microarrays which confirms that it is known in the art that in order "[t]o qualify as a microarray element, the element must be smaller than 1.0 mm." (*How are microarrays defined*, p. 7, Microarray Analysis, John Wiley & sons, Inc. NJ, 2003). The textbook also states that "earlier glass- and filter-based methods ... used large printed elements > 1 mm in diameter." (ibid).

Since Shuber does not teach or suggest each every element of claim 28 (as amended), and claims 29-33, 36-39, 41-43 and 46 depend from independent claim 28, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(b) be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 103

(a) Gilles et al. in view of Shuber

Claims 32-34 and 45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gilles et al. in view of Shuber et al.

Gilles is cited for disclosing alleles associated with diseases, but not the alleles associated with the claimed specific diseases. Shuber is cited for disclosing alleles associated with specific diseases.

As explained above in response to the 35 U.S.C. § 102 rejection, neither Gilles or Shuber teach each and every element of claim 28, as amended. In particular, neither Gilles or Shuber teach the probe mixture or the determination of genotype by "detecting [hybridization signal] at each distinct location on the microarray after a single round of hybridization" as specified in amended, independent claim 28.

As discussed above, Gilles and Shuber, by themselves or in combination, do not teach each and every limitation of claim 28, as amended. Therefore, Applicant respectfully requests withdrawal of these grounds for rejection of claims 32-34 and 45 which depend from independent claim 28.

(b) Gilles et al. in view of Brown

Claims 35 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilles et al. in view of Brown et al.

Brown is cited for disclosing microarrays comprising at least 1000 locations/cm^2. The Examiner argues that it would have been obvious to apply the array density taught by Brown to the microarray of Gilles to obtain the microarray density as claimed.

As discussed above, Gilles does not teach each and every element of claim 28. In particular, Gilles fails to teach the determination of genotype by "detecting [hybridization signal] at each distinct location on the microarray after a single round of hybridization" or the probe mixture as specified in amended, independent claim 28 as discussed above. Claims 35 and 44 depend from independent claim 28. Brown does not teach or suggest use of hybridization with oligonucleotide probes under conditions that are capable of discrimination at single nucleotide resolution. Thus, Brown also does not teach genotyping of an individual by "detecting [hybridization signal] at each distinct location on the microarray after a single round of hybridization."

Thus, Brown and Gilles, individually or in combination, do not teach each and every element of independent claim 28, from which claims 35 and 44 depend. Therefore, Applicant respectfully requests withdrawal of this ground for rejection.

(c) Gilles in view of Hames

Claim 40 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Gilles et al. in view of Hames et al.

Hames is cited for disclosing hybridization at about 10°C below the melting temperature.

As discussed above, Gilles does not teach each and every element of claim 28. In particular, Gilles fails to teach the determination of genotype by "detecting [hybridization signal] at each distinct location on the microarray after a single round of hybridization" or the probe mixture as specified in amended, independent claim 28 as discussed above. Hames also does not teach these limitations. Claim 40 depends from independent claim 28. Gilles and Hames, by themselves or in

combination, do not teach each and every limitation of claim 28. Therefore, Applicant respectfully requests withdrawal of this ground for rejection.

(d) Shuber in view of Drmanac

Claims 35 and 43-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shuber et al. in view of Drmanac.

Drmanac is cited for disclosing array densities of 1000 locations/cm^2.

As discussed above, Shuber does not teach each and every element of claim 28. In particular, Shuber fails to teach the determination of genotype by "detecting [hybridization signal] at each distinct location on the microarray after a single round of hybridization" or the probe mixture as specified in amended, independent claim 28 as discussed above. Drmanac also does not teach these limitations. Claim 35 and 43-45 depend from independent claim 28. Shuber and Drmanac, by themselves or in combination, do not teach each and every limitation of claim 28. Therefore, Applicant respectfully requests withdrawal of this ground for rejection.

(e) Shuber in view of Hames

Claim 40 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Shuber in view of Hames et al.

Hames is cited for disclosing hybridization at about 10°C below the melting temperature.

As discussed above, Shuber does not teach each and every element of claim 28. In particular, Shuber fails to teach the determination of genotype by "detecting [hybridization signal] at each distinct location on the microarray after a single round of hybridization" or the probe mixture as specified in amended, independent claim 28 as discussed above. Hames also does not teach these limitations. Claim 40 depends from independent claim 28. Shuber and Hames, by themselves or in combination, do not teach each and every limitation of claim 28. Therefore, Applicant respectfully requests withdrawal of this ground for rejection.

V. Citation of U.S. Patent No. 6,268,147 to Beattie et al.

The Examiner advised the Applicant during a telephone interview that Beattie et al. has been made of record in this application. However, the Examiner has not specified the grounds for rejection based on this reference. Therefore, Applicant is unable to respond to the citation of this reference at this time with specificity. Upon review of Beattie, Applicant does not find a teaching of all elements of independent claim 28, as amended. Beattie relates to "allele-specific" capture probes on a microarray for hybridization to target nucleic acids and labelled stacking probes for detecting hybridization. In particular, Beattie does not teach "incubating a microarray with a probe mixture" wherein (a) the "microarray contains a plurality of samples containing genotypes of interest with each sample in a distinct location," and (b) "detecting [hybridization of the probe mixture] at the distinct location on the microarray after a single round of hybridization ... genotypes the individual."

CONCLUSION

In light of the amendments and arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent and respectfully request the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.529492000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 29, 2004

Respectfully submitted,

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